Al-Mustaqbal University
College of Pharmacy
General Toxicology
4th stage
Lecture: 5

Toxic Response on Kidney

WEAAM J. ABBAS

Functional Anatomy

✓The functional integrity of the mammalian kidney is vital to total body homeostasis because the kidney plays a different function .

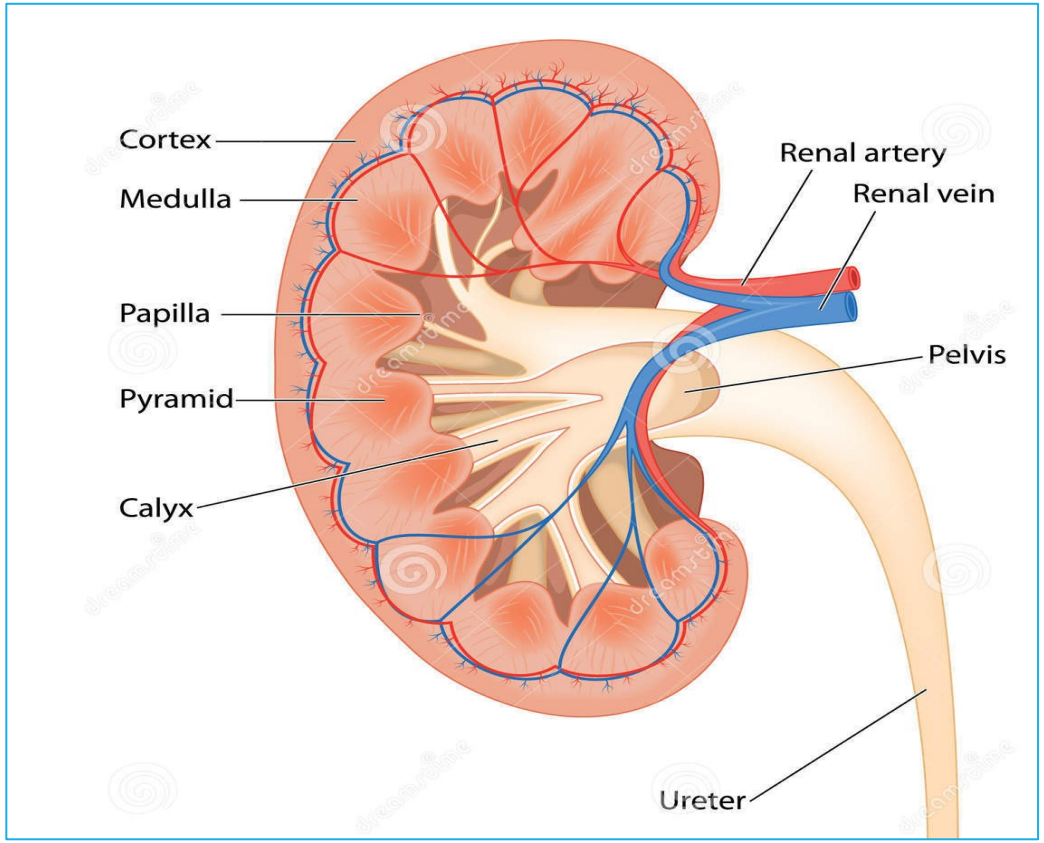
A toxic insult to the kidney therefore could disrupt any or all of these functions. Renin system ,…

7 Functions of the Kidneys

A WET BED

- **A** ACID-base balance maintaining
- **W** WATER balance maintaining
- **E** Electrolyte balance
- **T** TOXIN removal
- **B** BLOOD Pressure control
- **E** Erythropoietin making
- **D** D Vitamin metabolism

Functional Anatomy



Schematic of the human kidney

Functional Anatomy

✓**Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas:**

1. **Cortex major portion of the kidney (90%) from blood flow**
2. **Medulla (6% to 10%)**
3. **Papilla(1% to 2%)**

Functional Anatomy

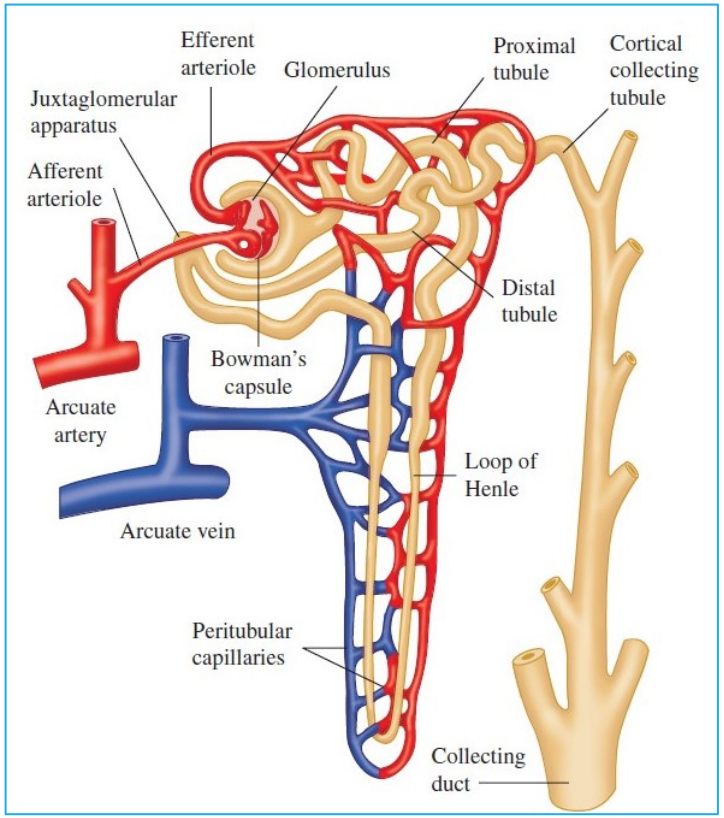
- ✓Thus, when a **blood-borne toxicant** is delivered to the kidney, a **high percentage** of the material will be delivered to the **cortex** and will have a greater **opportunity** to influence **cortical** rather than **medullary or papillary** functions.

- ✓However, **medullary** and **papillary** tissues are exposed to **higher luminal** concentrations of **toxicants** for **prolonged** periods of time, a consequence of the more concentrated tubular fluid and the more sluggish flow of blood and filtrate in these regions.

Functional Anatomy

✓**The functional unit of the kidney, the nephron, may be considered in three portions:**

1. **The vascular element**
2. **The glomerulus**
3. **The tubular element**



Acute Kidney Injury

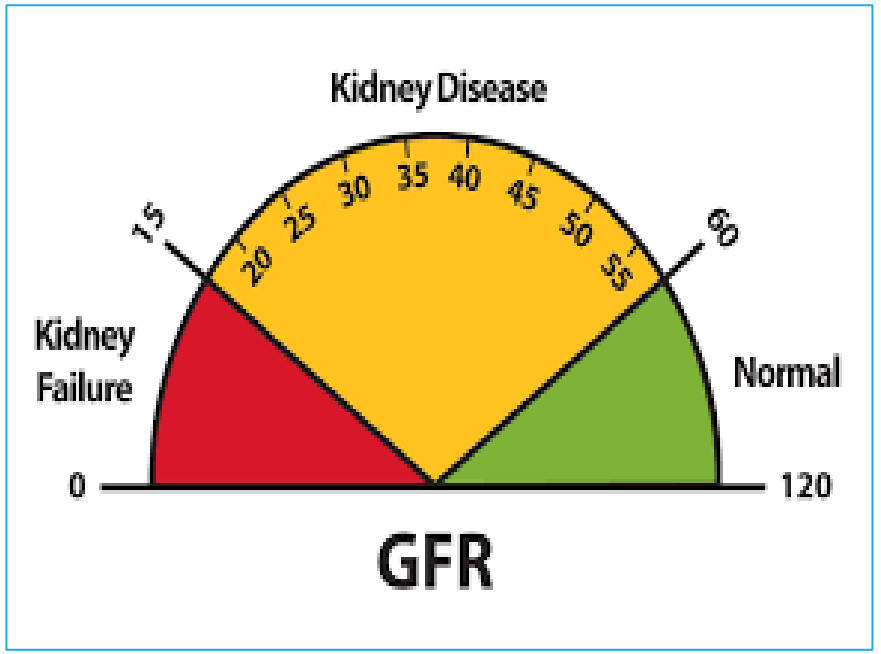
- ✓AKI is one of the most common manifestations of nephrotoxic damage.
- ✓AKI is a group of syndromes that comprises multiple causative factors with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.
- ✓AKI classification is based on the extent of serum creatinine increases or changes in urine output.

Acute Kidney Injury

✓**GFR** is equal to the **total filtration rates** of the functioning **nephrons** in the kidney.

✓GFR is considered the optimal way to measure **kidney function** and it depends on four factors:

1. Adequate blood flow to the glomerulus
2. Adequate glomerular capillary pressure
3. Glomerular permeability
4. Low intratubular pressure.



GFR in ml/min/1.73m²

Acute Kidney Injury

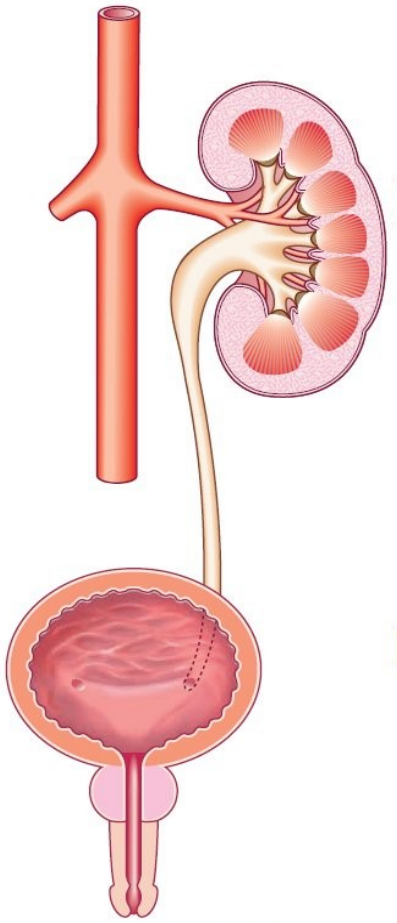
✓**Any decline in GFR is complex and may result from:**

1. **Prerenal factors:** 55% to 60% of patients

2. **Intrarenal factors:** 35% to 40% of patients

✓**Like glomerulonephritis, tubular cell injury, death, and loss; renal vasculature damage; and interstitial nephritis.**

3. **Postrenal factors:** less than 5% of patients



PRE-RENAL

Impaired perfusion:
- Cardiac failure
- Sepsis
- Blood loss
- Dehydration
- Vascular occlusion

RENAL

Glomerulonephritis
Small-vessel vasculitis
Acute tubular necrosis
- Drugs
- Toxins
- Prolonged hypotension

Interstitial nephritis
- Drugs
- Toxins
- Inflammatory disease
- Infection

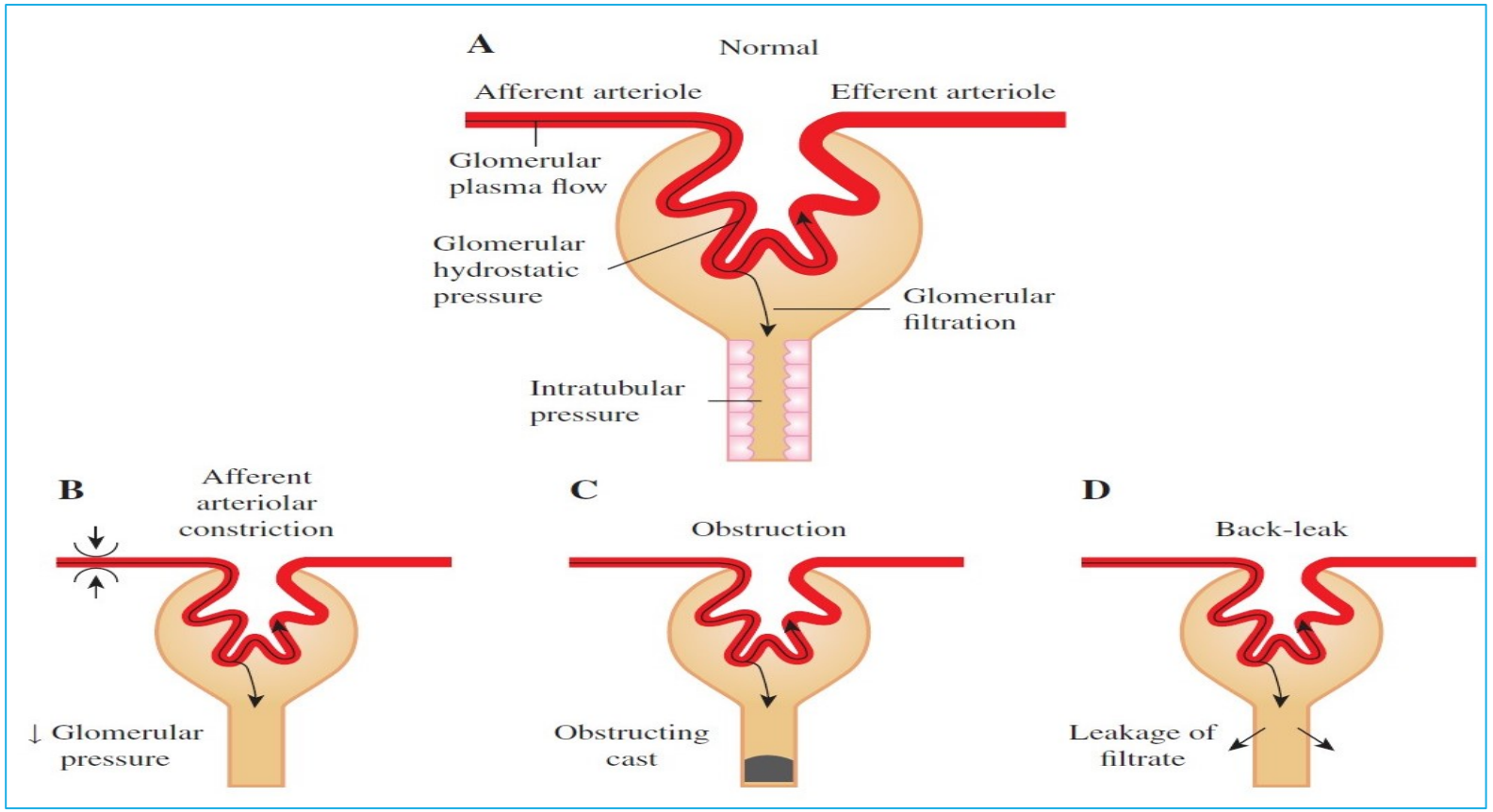
POST-RENAL

Urinary calculi
Retroperitoneal fibrosis
Benign prostatic enlargement
Prostate cancer
Cervical cancer
Urethral stricture/valves
Meatal stenosis/phimosis

Causes of acute kidney injury.

Source : Davidsons Essentials of Medicine, 2e

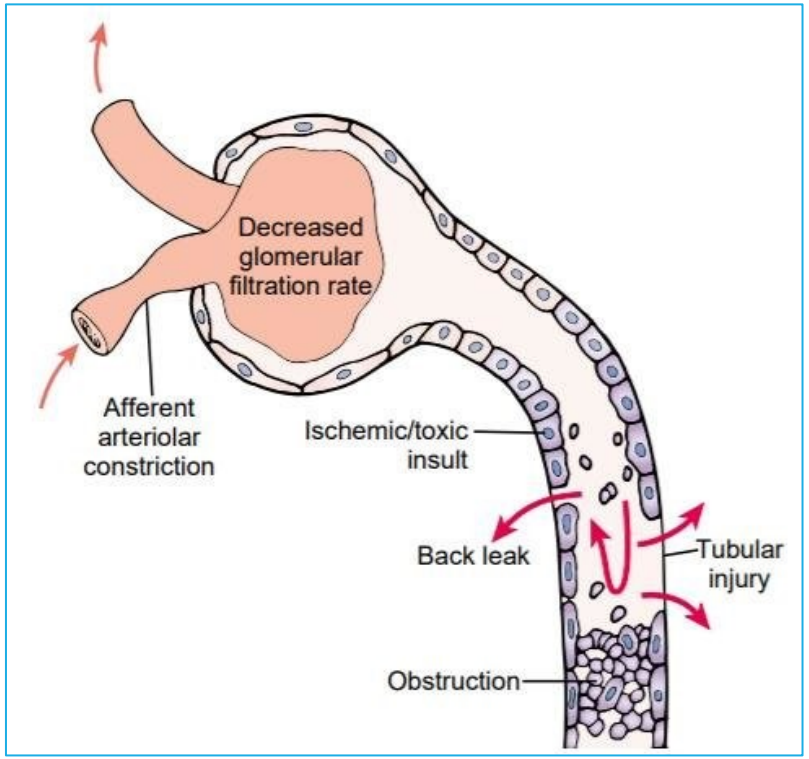
Acute Kidney Injury



Mechanisms of reduction of the GFR.

Acute Kidney Injury

- ✓If a chemical causes tubular damage directly, then tubular casts can cause tubular obstruction, increased tubular pressure, and decreased GFR.
- ✓The tubular damage may result in epithelial cell death/loss, leading to a back leak of glomerular filtrate and a decrease in GFR.



Casts obstruction & back leak of glomerular filtrate

Acute Kidney Injury

- ✓ If a chemical causes intrarenal vascular damage with hemodynamic alterations → vasoconstriction. →
- ✓ (medullary hypoxia) → tubular damage and/or
- ✓ ↓ perfusion pressure,
- ✓ ↓ glomerular hydrostatic pressure,
- ✓ and finally ↓ GFR.)
- ✓ If a chemical causes intrarenal inflammation, then tubular and vascular damage may follow with decreases in GFR.

Adaptation Following Toxic Insult

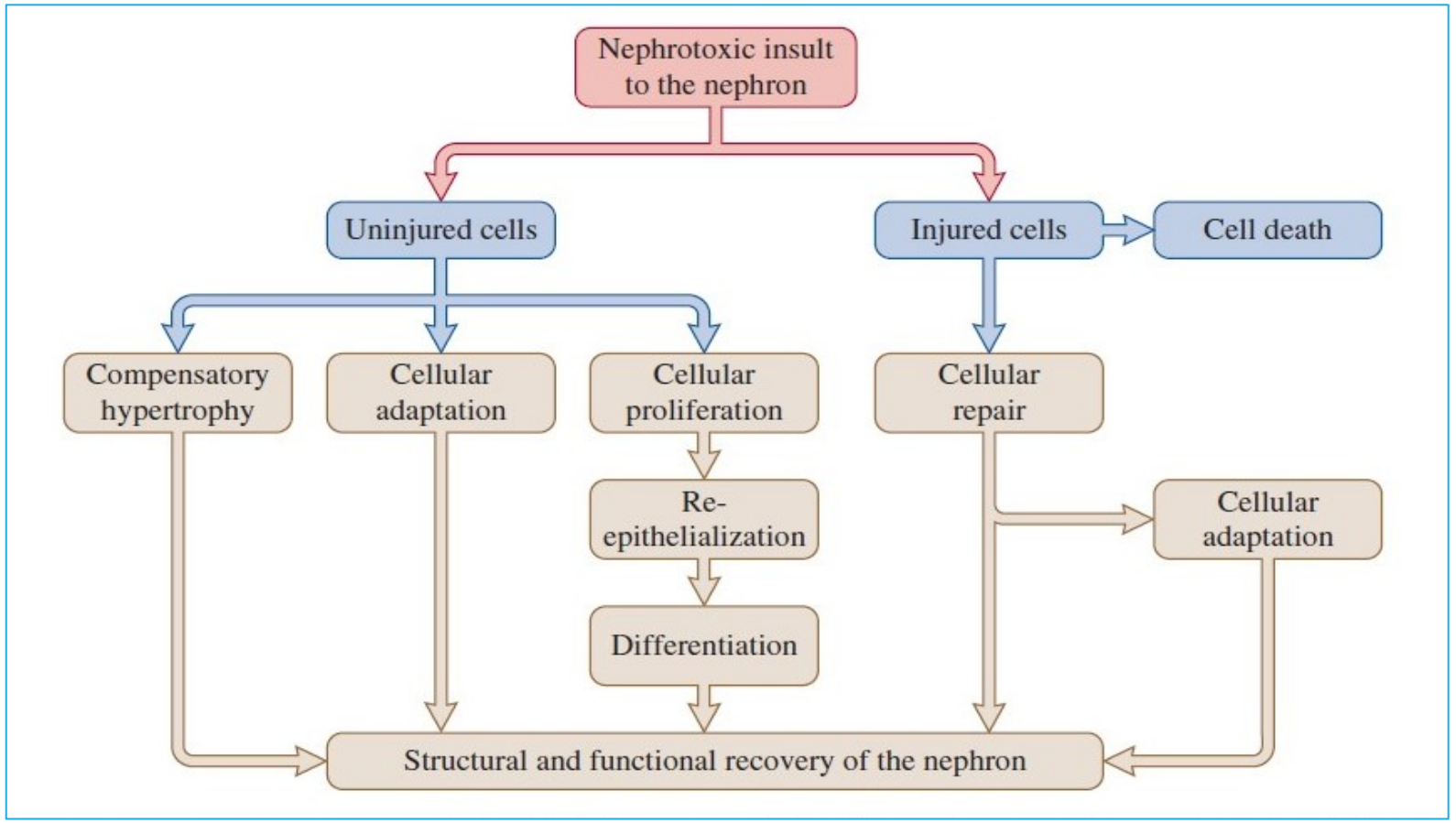
- ✓**Fortunately, the kidney has a remarkable ability to compensate for a loss of renal functional mass.**
- ✓**Renal studies have revealed that following unilateral nephrectomy, the GFR of the remnant kidney increases by approximately 40% to 60%.**
- ✓**This effect is associated with early compensatory increases in glomerular plasma flow rate and glomerular hydraulic pressure.**

Adaptation Mechanisms

1. **The cells that are nonlethally injured may undergo cell repair and/or adaptation and contribute to the recovery of the nephron.**

2. **In addition, there is a population of cells that are uninjured may undergo compensatory hypertrophy, adaptation, and proliferation.**

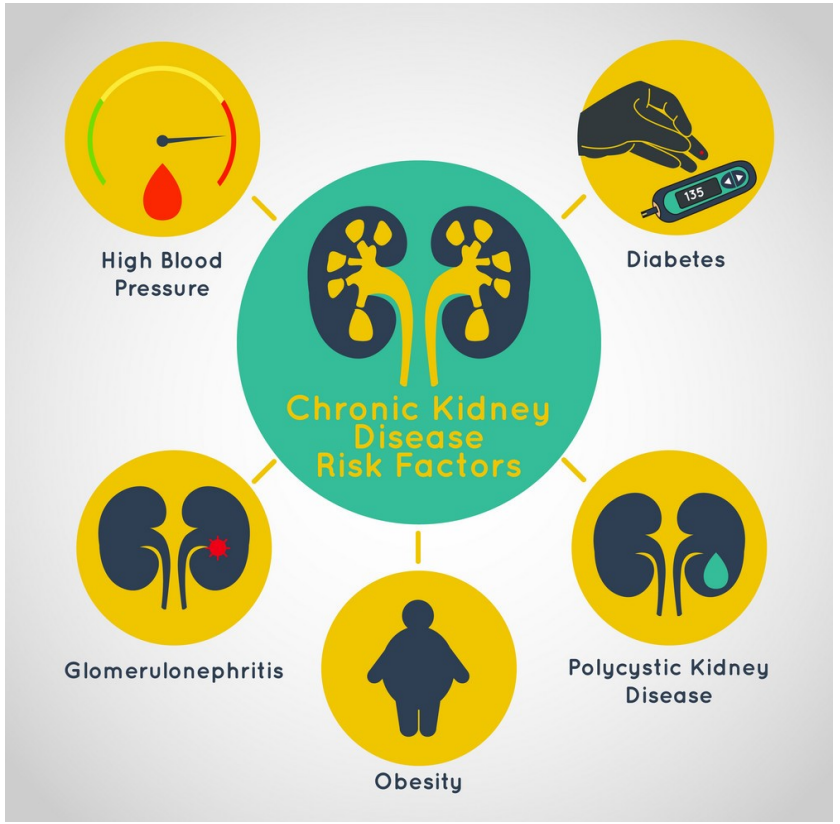
Adaptation Mechanisms



The response of the nephron to a nephrotoxic insult

Chronic Kidney Disease

- ✓It is generally thought that progression to chronic kidney disease (CKD) and end-stage renal failure is not simply a function of a primary renal insult.
- ✓It is related to secondary pathophysiologic processes triggered by the initial injury.



Chronic Kidney Disease

- ✓**Deterioration** of renal function may occur with **long-term exposure** to a variety of **chemicals** (e.g., analgesics, lithium, and cyclosporine).

- ✓The **progression** of chronic renal disease, for example, maybe a **consequence** of the glomerular hemodynamic response to renal injury.

Chronic Kidney Disease

- ✓**Following nephron loss, there are adaptive increases in glomerular pressures and flows that increase the single-nephron GFR of remnant viable nephrons.**

- ✓**Although these compensatory mechanisms serve to maintain whole-kidney GFR, evidence has accumulated to suggest that, with time, these alterations are maladaptive and faster the progression of renal failure.**

Incidence and Severity of Toxic Nephropathy

- ✓ **A wide variety of drugs, environmental chemicals, and metals can cause nephrotoxicity.**
- ✓ **Nephrotoxicity is a recognized clinical liability of certain classes of drugs, in particular:-**

antibiotics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers,

analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast media,

and anticancer agents.

Incidence and Severity of Toxic Nephropathy

- ✓Approximately 70% of the patients presenting with drug-induced AKI were non oliguric.
- ✓The pathologic findings revealed acute tubular necrosis in 60%, approximately 50% recovered completely.
- ✓The consequences of AKI can be profound, as permanent renal damage may result and

dialysis or renal transplantation may be required.

Incidence and Severity of Toxic Nephropathy

- ✓CKD leading to end-stage renal failure has been associated with long-term abuse of analgesics.
- ✓The incidence of analgesic nephropathy has been reported to be as high as 20% to 25%.
- ✓Other chemicals, such as lithium, cyclosporine, NSAIDs, lead, and cadmium may produce chronic tubulointerstitial nephropathy with progressive loss of renal function.

Susceptibility of the Kidney to Toxicity

- ✓The **susceptibility** of the kidney to the **toxic effects** of chemicals can be **attributed** to its **unique physiologic and anatomic features**.
- ✓As kidneys **constitute** only **0.5%** of total body mass, they **receive** about **20% to 25%** of the resting **CO**.
- ✓Consequently, **any** drug or chemical in the systemic circulation will be **delivered** to these organs in **relatively high amounts**.

Susceptibility of the Kidney to Toxicity

- ✓The processes involved in forming **concentrated urine** also serve to **concentrate** potential toxicants in the tubular fluid.
- ✓As water and electrolytes are **reabsorbed** from the glomerular filtrate, chemicals in the tubular fluid may be **concentrated**, thereby driving **passive diffusion** of toxicants into tubular cells.
- ✓Therefore, a **nontoxic** concentration of a chemical in the **plasma** may reach **toxic** concentrations in **the kidney**.

Susceptibility of the Kidney to Toxicity

- ✓ **Also, renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney to toxic injury.**

- ✓ **In addition to intrarenal factors, the incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoactive substances.**

Site-Selective Injury

- ✓Many **nephrotoxicants** have their primary effects **on discrete segments** or **regions** of the nephron. Why ?
- ✓For example, the **proximal tubule** is the primary target for most nephrotoxic antibiotics, antineoplastics, halogenated hydrocarbons, mycotoxins, and heavy metals,
- ✓Whereas the **glomerulus** is the primary site for immune complexes, the **loop of Henle/collecting ducts** for fluoride ions,
- ✓**medulla/papilla** for chronically consumed analgesic mixtures.

Glomerular Injury

- ✓The glomerulus is the initial site of chemical exposure within the nephron, and a number of nephrotoxicants produce structural injury to this segment.
- ✓In certain instances, chemicals alter glomerular permeability to proteins by altering the size- and charge-selective functions. Eg doxorubicin target glomerular epithelial cells
- ✓Cyclosporine, amphotericin B, and gentamicin are examples of chemicals that impair glomerular ultrafiltration without significant loss of structural integrity and decrease GFR.

Glomerular Injury

- **Because of its polycationic nature, the aminoglycoside gentamicin interacts with the anionic sites on the endothelial cells, decreasing Kf, and GFR.**

- **Meanwhile, cyclosporine not only causes renal vasoconstriction and vascular damage but also is injurious to the glomerular endothelial cell.**

Proximal Tubular Injury

- ✓**The proximal tubule is the most common site of toxicant-induced renal injury.** 
- ✓**The reasons for this relate in part to the selective accumulation of xenobiotics into this segment of the nephron.**
- ✓**More importantly, tubular transport of organic anions and cations, low-molecular-weight proteins and peptides, GSH conjugates, and heavy metals is localized primarily if not exclusively to the proximal tubule.**

Proximal Tubular Injury

- ✓**Proximal tubular cells appear to be more susceptible to ischemic injury than distal tubular cells.**
- ✓**Therefore, the proximal tubule will likely be the primary site of toxicity for chemicals that interfere with RBF, cellular energetics, and/or mitochondrial function.**

Distal Tubular Structures Injury

- ✓ Injury is an infrequent occurrence.
- ✓ Functional abnormalities such as impaired concentrating ability and/or acidification defects.
- ✓ Drugs such amphotericin B ,cisplatin, and methoxyflurane.
- ✓ May induces an ADH-resistant polyuria

Distal Tubular Structures Injury

✓**The mechanisms mediating cisplatin-induced polyuria occur in two phases:**

1. **The first phase is responsive to vasopressin and inhibitors of prostaglandin synthesis.**
2. **The second phase is not responsive to vasopressin or prostaglandin synthesis inhibitors but is associated with decreased papillary solute content.**

Papillary Injury

✓**factors may contribute to this site-selective injury, including:**

1. **High papillary concentrations of potential toxicants**
2. **Inhibition of vasodilatory prostaglandins**

✓**These two factors compromise RBF to the renal medulla/papilla, resulting in tissue ischemia.**